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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,521	08/23/2002	Mikael Simons	100564-00111	7321

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EXAMINER	
MCINTOSH III, TRAVISS C	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 09/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,521	SIMONS ET AL.	
	Examiner	Art Unit	
	Traviss C McIntosh	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,22 and 24-40* is/are pending in the application.

4a) Of the above claim(s) *9-12 and 32-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 13-19, 22, and 24-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed April 30, 2004 has been received, entered into the record, and carefully considered. The following information provided in the amendment affects the instant application by:

Claims 1-14, 16-19, 22, and 24-31 have been amended.

Claims 20-21, and 23 have been canceled.

Remarks drawn to rejections of Office Action mailed December 30, 2003 include:

Claim objections: which have been overcome by applicant's amendments and have been withdrawn.

112 2nd paragraph rejections: which have been overcome in part by applicant's amendments and have been withdrawn in part.

103(a) rejections: which have been maintained for reasons of record.

An action on the merits of claims 1-19, 22, and 24-31 is contained herein below. The text of those sections of Title 35, US Code which are not included in this action can be found in a prior Office action.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e)

has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 29, 2004 has been entered.

It is noted that in the response filed by applicants on April 30, 2004, applicants had requested that the finality of the previous office action be withdrawn as the references Brown and Rietveld were newly cited. However, these references were cited in response to the amendment filed, and thus necessitated by the amendment, and thus the finality is deemed proper. However, the finality is currently being withdrawn pursuant to 37 CFR 1.114, as set forth supra.

Additionally, applicants argue that previously added claims 32-40 are improperly withdrawn as the search for the original claims would have entailed a search for the compounds recited in the composition claims. However, the examiner notes that independent claim 32 requires at least one unsaturated sphingosine or ceramide, which the method claims do not require. As set forth in the previous office action, applicants have already received an action on the merits of the methods, which do not require said unsaturated moiety, and thus the withdrawal of claims 32-40 is maintained as proper.

Newly amended claims 9-12 are directed to inventions that are independent or distinct from the invention originally filed for the following reasons: the claims originally filed were drawn to a method of modulating the sphingolipid-cholesterol microdomains in a patient, claim 9 as amended is drawn to a method of changing membrane transport, signal transmission, cell

adhesion properties, and/or enzymatic processes in a patient, claim 10 as amended is drawn to a method of changing the proteolysis of the amyloid precursor protein of Alzheimer's disease or modifying a prion protein in a patient, claim 11 is drawn to a method of preventing phagocytosis of bacteria and parasites in mammalian cells, and claim 12 is drawn to a method of preventing the uptake of viruses into mammalian cells and/or their transport or release. These methods are seen to be patentably distinct from the methods as originally claimed.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 9-12 have been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. It is noted that these claims were originally examined because they were objected to for not further limiting the claim from which they depended.

Claim Rejections - 35 USC § 112

Claims 1-8, 13-19, 22, and 24-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

All claims which claim a "derivative", for example claims 1-6, 8, 14, and 15, are indefinite. In the absence of the identity of moieties intended to modify an art recognized chemical core, either structurally, or by chemical name, the identity of a derivative would be difficult to ascertain. In the absence of said moieties, the claims containing the term "derivative"

are not described sufficiently to distinctly point out that which applicant intends as the invention. Applicant's arguments filed April 30, 2004 have been fully considered but they are not persuasive. Applicants argue that the term derivative is defined in the specification, in particular on page 5, lines 20-24 and page 7, lines 4-7, and thus, one of ordinary skill in the art would understand the term derivative and the scope of the rejected claims. However, the examiner notes that in the examination process, it is proper to use the specification to interpret what applicant intends by a word or phrase recited in the claims, but it is **not** proper to read these limitations appearing in the specification into the claim when these limitations are not recited in the claim. See *In re Paulsen,* 30 F. 3d 1475, 1480, 31 USPQ2d 1671, 1674 (Fed. Cir. 1994). Moreover, applicants definition of derivative uses such phrases as "preferably contain…", and "formed in only one reaction step and are chemically closely related…" are not seen as clear and precise definition of **what is** intended by a derivative, but optional language which describes alternatively what a derivative **might be**. If applicants are relying on the specification for a definition, providing an exemplary definition is not adequate for that which 112 2nd paragraph requires, which is a clear and concise definition. Moreover, applicants argue that the examiner is imposing a requirement that applicant prepare an application which is void of any generic terms. However, the examiner is no requiring that, the examiner is requiring that applicants provide claims which are void of any indefinite terms. Moreover, applicants argue that the purpose of 112 2nd paragraph is to ensure that the claim language is sufficiently precise so that a person of skill in the art can determine the boundaries of the claim. However, as the claims read, one of skill in the art would not be able to ascertain the boundaries of the claim. It is unclear as to what a "chemically similar" compound would be. To what level of similarity, and in what chemical

way are they similar, each molecule having the same pH, or being soluble in water, or have free hydroxy groups for reactivity? One of skill in the art would not be able to determine the metes and bounds of the claim. Applicants should include in the claims that which they intend as their invention. All claims which contain "derivative" but do not explicitly disclose in a clear and concise manner that which is intended as a derivative are indefinite.

Claim Rejections - 35 USC § 103

The rejection of claim 15 under 35 U.S.C. 103(a) as being unpatentable over Ladisch et al. (US Patent 4,551,449) is maintained for reasons of record.

Claim 15 of the instant application is drawn to a method of modulating the sphingolipid-cholesterol microdomain in a patient by administering a dose from 3 mg to 30 mg per kg body weight of a composition comprising gangliosides and/or cholesterol to a patient.

Ladisch et al. disclose that the lipid composition of the extracellular environment can alter (modulate) the lipid composition of the cell membrane and modulate certain cellular processes including cell proliferation wherein micelles of lecithin and/or cholesterol are used (column 1, lines 33-43). Additionally, Ladisch et al. teach that lecithin can be replaced by other phospholipids.

It would be obvious to one of ordinary skill in the art at the time the invention was made to administer a cholesterol/ganglioside composition to modulate the cholesterol-lipid microdomain of the cell membrane because Ladisch teach that altering the extracellular amounts of lecithin and/or cholesterol modulate the lipid composition of the cell membrane. One of ordinary skill in the art would know how to perform tests to determine which ranges of

lipid/cholesterol would be effective and would expect the dosage administered to affect the microdomain associated with the lipids administered.

Applicant's arguments filed April 30, 2004 have been fully considered but they are not persuasive. Applicants argue that Ladisch et al. do not teach a modulation of the sphingolipid-cholesterol microdomain by administering gangliosides, derivatives thereof, and/or cholesterol derivatives. However, it is noted that the Ladisch et al. reference is cited to simply show that it is known in the art that the administration of lipids and/or cholesterol can alter the lipid composition of the cell membrane, and thus modulate certain cellular processes. Ladisch does not delimit the sphingolipid-cholesterol microdomain, and the sphingolipid-cholesterol microdomain is a part of the cell wall, thus administering lipids would indeed modulate said domains. That is, the administration of lipids which therein modulates the lipid concentration of the cells membrane is known in the art. Applicants claim a method of modulating a portion of the cell membrane (the sphingolipid-cholesterol microdomain) by administering lipids or cholesterol which are associated with that portion of the membrane. One of ordinary skill in the art would find it obvious to administer the sphingolipids of the microdomain because Ladisch teach that the lipid composition of the extracellular environment can alter (modulate) the lipid composition of the cell membrane, thus modulating the microdomains. Moreover, applicants argue that Ladisch teaches administration of cholesterol, and not cholesterol derivatives. However, without clearly indicating which specific compounds are intended to be administered, the broad recitation of derivatives would obvious to one of skill in the art. There is well established case law which states that for example, an adjacent homolog to cholesterol would be obvious absent unexpected results. See ***In re Henze, 85 USPQ 261, 263, (CCPA 1950)*** for example.

The rejection of claims 1-8, 13-19, 22, and 24-31 under 35 U.S.C. 103(a) as being unpatentable over the combination of Brown et al. (Sphingolipid organization in biomembranes: what physical studies of model membranes reveal", Journal of Cell Science, vol. 111, pgs 1-9, 1998) and Rietveld et al. ("The differential miscibility of lipids as the basis for the formation of functional membrane rafts", Biochimica et Biophysica Acta, vol. 1376, pgs. 467-479, 1998) in view of Ladisch et al. (US Patent 4,551,449) is maintained for reasons of record.

Claim 1 is drawn to a method of modulating the sphingolipid-cholesterol microdomain in a patient by administering at least one ganglioside, ganglioside derivative, or cholesterol derivative to the patient. Claim 7 limits the ganglioside to a bovine brain ganglioside, GM_1, GM1a, GD1a, GD1b, GD3, GM2, GM3, GQ1a, GQ1b, or a globoside. Claim 8 provides that a cholesterol derivative is administered; claim 13 provides that a ganglioside is administered, and claim 14 provides that a ganglioside derivative is administered. Claim 15 provides that 3-30mg of active agents per kg body weight of the patient is administered. Claim 16 provides that the ganglioside is a sphingosine or ceramide derivative is administered, and claim 17 limits the derivative to one comprising at least one monosaccharide unit. Claim 18 provides that a sphingosine derivative is administered, and claim 19 provides that the ganglioside is a ceramide derivative represented structurally in claim 19. Claims 24 and 25 limit the fatty acid and alkyl chain to C_8-C_{24} residues. Claim 22 provides that one of various functional groups can be substituted or added on the backbone chain. Claim 26 provides that the cholesterol derivative is cholesterol sulfate or thiosulfate, and claim 27 provides that at least one substituted or added organic group is on the cholesterol derivative, wherein claim 28 provides guidance as to what

organic groups are optionally added. Claim 29 provides that the cholesterol derivative comprises an oligopeptide, oligonucleotide, amino acid, monosaccharide, disaccharide, or polysaccharide. Claim 30 limits the ganglioside derivative to an unsaturated sphingosine or ceramide containing unsaturated or short fatty acids. Claim 31 provides that the cholesterol derivative is cholesterol sulfate.

Brown et al. teach that purely physical interactions between the lipids promote membrane domain formation, and that the ability of the domains, or rafts, to laterally segregate proteins during the sorting process is attributed to the differences in the physical environment within the lipid domains themselves, as compared to other membrane regions (page 1, column 2). Brown et al. teach that cholesterol can promote phase separation and change the physical properties of the resulting sphingolipid-cholesterol enriched phases (page 2, second column, 1st full paragraph). Adding cholesterol increases the lipid packing densities of the sphingolipids which affect their in-plane elasticity. Moreover, cholesterol absence in the microdomain is shown to affect the physical nature of the microdomain and without cholesterol, the sphingolipid hydrocarbon chains would be rigid due to their gel and or lamellar crystalline character. In contrast, the liquid-ordered state created by high cholesterol concentrations would provide a domain environment that is tightly packed and of low in-plane elasticity (page 6, column 2). Brown further teaches that such an environment could be regulated to facilitate the diffusion of GPI-anchored proteins (or other proteins) into or out of such microdomains (page 6, column 2). Moreover, Brown et al. teach of the various sphingolipid structures associated with the sphingolipid-cholesterol microdomains, and that acyl chains of 234 carbons are common in bovine brain cerebrosides and in sulfatides and predominate in brain sphingomyelin and gangliosides (page 4, column 1). What

is not taught is to specifically administer gangliosides or cholesterol to modulate the sphingolipid-cholesterol microdomains.

Rietveld et al. teaches that GPI-anchored proteins are associated with the Triton detergent insoluble portion of the membrane, which comprises sphingolipids and cholesterol (page 468, column 2), and that there are additional cytoplasmic face associated signaling molecules associated with the raft. The majority of sphingolipids is composed of a ceramide which commonly consists of a sphingosine, a dihydrosphingosine, or a phytosphingosine in amide linkage to a long chain fatty acid which is often hydroxylated (page 469, column 1 and structures on column 2). Moreover, Rietveld et al. teach that a matter of crucial importance for biological functions is the size and connectivity of lipid microdomains (page 472, column 1) and that cholesterol could stabilize domains and increase their size in a concentration-dependent manner (page 472, column 2). Furthermore, most detergent insoluble glycolipids-enriched complex associated proteins will dissociate from the lipids after cholesterol depletion (page 473, column 2). Moreover, Rietveld et al. teach that GPI-anchored proteins (which are associated with sphingolipid-cholesterol microdomains) can interact with *src*-like kinases such as $p56^{lck}$, which is critical for T-cell development and activation (page 474, column 1). Moreover, Rietveld et al. teach that the integrity of the rafts is critically dependent upon cholesterol (page 475, column 2). What is not taught is to specifically administer gangliosides or cholesterol to modulate the sphingolipid-cholesterol microdomains.

Ladisch et al. disclose that the lipid composition of the extracellular environment can alter (modulate) the lipid composition of the cell membrane and modulate certain cellular processes including cell proliferation wherein micelles of lecithin and/or cholesterol are used

(column 1, lines 33-43). Additionally, Ladisch et al. teach that lecithin can be replaced by other phospholipids.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer sphingolipids or cholesterol molecules to a patient in need of modulation of the sphingolipid-cholesterol microdomain, wherein the administered sphingolipids and or cholesterol would modulate the lipid composition of the microdomain of the cell, as taught by Ladisch. One would be motivated to administer sphingolipids and or cholesterol to modulate the sphingolipid-cholesterol microdomain, as Ladisch teaches that extracellular lipids can alter the lipid concentration of the cell membrane, and Reitveld et al. teaches that a matter of crucial importance for biological functions is the size and connectivity of the lipid microdomains. One of ordinary skill in the art, with these references before them, would find it obvious to administer art recognized lipids, which are taught to be associated with the sphingolipid-cholesterol microdomains, and that these lipids would modulate the lipid membranes which they are associated with, as this class of compounds is known to modulate the lipid membrane when administered. The prior art teaches the lipid structure of the microdomains, and the proteins which are associated therewith, and that when the structure is compromised, the proteins association with the raft is compromised, and when lipids are administered, the lipid membrane is modulated.

Applicants argue that none of Ladisch, Brown, or Rietveld teach to administer gangliosides, ganglioside derivatives, or cholesterol derivatives. Moreover, applicants argue that

Reitveld indicates that addition of cholesterol would stabilize the microdomains, not increase the detergent solubility of the proteins in the domains. However, there is well established case law which states that for example, an adjacent homolog to cholesterol would be obvious absent unexpected results. See ***In re Henze, 85 USPQ 261, 263, (CCPA 1950)*** for example. Thus, it would be obvious to administer a generic undefined derivative of cholesterol to "modulate", in any way, and any amount, the microdomains with these references before them.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Traviss C McIntosh whose telephone number is 703-308-9479. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 703-308-4624. The fax phone number for the organization where this application or proceeding is assigned is 703-305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

It is noted that after February 1st, 2004, Examiner McIntosh can be reached at (571) 272-0657 and Mr. Wilson can be reached at (571) 272-0661.

Traviss C. McIntosh III
December 18, 2003

James O. Wilson
Supervisory Patent Examiner
Art Unit 1623

BRUCK KIFLE, PH.D.
PRIMARY EXAMINER